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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,787	09/23/2005	Lea Eisenbach	EISENBACH4A	8693

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EXAMINER	
BRISTOL, LYNN ANNE	

ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,787	EISENBACH ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-7,9 and 12-61* is/are pending in the application.

4a) Of the above claim(s) *24-29,46-58,60 and 61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-7, 9, 12-23, 30-45 and 59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/16/05; 9/23/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 3-7, 9 and 12-61 are all the pending claims for this application.

Election/Restrictions

2. Applicant's election with traverse of Groups III (Claims 1-7, 9, 12-23, 30-45 and 59) in the reply filed on 5/3/07 is acknowledged.

The traversal is on the ground(s) that because SEQ ID NO: 41 (STEAP-3) has been deleted from Claim 1, the Afar reference cited in the lack of unity restriction of 4/12/07 no longer defeats the special technical feature in generic claim 1. Thus, elected Group III should be rejoined with Groups X and XIII.

This is not found persuasive because generic Claim 1 does not specifically exclude or negatively recite that a peptide cannot be obtained from SEQ ID NO: 41 (STEAP-3). Rather, the claim is now so broadly generic for any peptide obtained from any human colon carcinoma, that in addition to Afar still reading on the claims, there are innumerable other references that teach the class of peptides derived from human 1-8D inducible genes.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 24-29, 46-58, 60 and 61 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 5/3/07.

4. Claims 1, 3-7, 9, 12-23, 30-45 and 59 are all the claims under examination.

Priority

5. Priority claims to U.S. Provisional Application No. 60/403,657 (filed 8/16/02) for SEQ ID NOs: 27, 58, 59, 60 and 61 is acknowledged.

Information Disclosure Statement

6. The non-patent literature references cited in the IDS' of 2/16/05 and 9/23/05 have been considered and entered.

Specification

7. The disclosure is objected to because of the following informalities:

a) The specification is objected to because it does not provide sequence identifiers for the following sequences pursuant to 37 CFR 1.821 (c) and/or (d):

PI-P2-P3-P4-P5-P6-P7-P8-P9 (see p. 30).

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 3, 4, 7, 9 and 12-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the MHC-Class I binding, CTL-inducing peptide epitopes of Table 1, the inventive colo-rectal carcinoma-gene derived

peptides in Tables 3 and 5, does not reasonably provide enablement for any peptide isolated from any protein expressed by any polynucleotide from a human colon carcinoma cell where the peptide has the ability to bind MHC Class I *and* elicit a peptide-specific CTL response and where the peptide is optionally includes at least one non-natural modification. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to practice the invention as claimed.

Nature of the Invention

Claims 1, 3, 4, 7, 9 and 12-14 are drawn to MHC-class I binding, CTL-inducing peptides of from 8 to 10 residues in length and derived from proteins encoded by a polynucleotide expressed in human colon carcinoma cells and the peptide optionally include at least one non-natural modification, where the second residue from the N-terminus and the C-terminal residue are hydrophilic or hydrophobic or neutral, hydrophobic or aliphatic natural amino acids, where the protein is encoded by a polynucleotide coding sequence of human 1-8D inducible gene, where the peptide has

amino acid sequence SEQ ID NO:27, where the peptide is derived from a protein encoded by a polynucleotide overexpressed in human colon carcinoma calles, wherein when the second residue from the N-terminus of the peptide and the C-terminal residue of the peptide are neutral, hydrophobic or aliphatic natural amino acid residues, they are replaced with neutral, hydrophobic or aliphatic non-natural amino acid residues, where the peptide binds to HLA-A2, where the peptide includes a non-natural modification such as a peptide modification, a semi peptide modification, a cyclic peptide modification, a N-terminus modification, a C-terminus modification, a peptide bond modification, a backbone modification and a residue modification.

Disclosure in the Specification

The specification discloses general classes of MHC-class I binding, CTL-inducing peptides in Table 1. The inventive peptides shown to have MCH Class-I binding and CTL-inducing activity in vitro are those of SEQ ID NO: 6-27 (table 3), and the peptides shown to have putative MHC-Class I binding are of SEQ ID NO:29-55. None of the peptides are disclosed as being modified to contain a non-natural amino acid such as a peptide modification, a semi peptide modification, a cyclic peptide modification, a N-terminus modification, a C-terminus modification, a peptide bond modification, a backbone modification and a residue modification. The specification teaches peptide conjugates to other molecules or compounds (pp. 29 and 35). Thus the specification is not enabling for the breadth of the peptides encompassed by the instant claims. One skilled in the art would be left to identify not only the infinite polynuleotides expressed by the human colon carcinoma and to clone those nucleotides in order to identify proteins,

but would then be required to identify the peptide epitopes that meet all of the limitations of the claims. One skilled in the art could not determine which of the infinite combination of modifications could be made to any class much less individual peptide based on the specification alone, because the specification does not define the specific positions and regions of the peptides which can be predictably modified and which regions are critical and the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Status of the Art for Peptide Variants

Furthermore, protein biochemistry is one of the most unpredictable fields in biochemistry. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252). Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin. Schwartz et al, Proc Natl Acad Sci USA Vol 84:6408-6411 (1987). Removal of the amino terminal histidine of glucagon substantially decreases the ability of the molecule to bind to its receptor and activate adenylate cyclase. Lin et al Biochemistry USA Vol 14:1559-1563 (1975).

These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein.

Therefore, in view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad of molecules encompassed in the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

9. Claims 15-23 and 30-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

See the interpretation of Wands as discussed supra.

Nature of the Invention/ Skill in the Art

Claims 15-23 are drawn to pharmaceutical compositions for treating or inhibiting the development of colon cancer with the inventive MHC-class I binding, CTL-inducing peptides and further comprising vaccine compositions and cellular vaccine compositions. Claims and 30-45 are drawn to pharmaceutical compositions for treating or inhibiting the development of colon cancer with a protein encoded by human 1-8D interferon inducible gene, MHC class I, CTL-inducing peptides of the same or polynucleotides encoding the same.

In order to practice the invention, one of skill in the art would be required to understand the clinical management of human colon carcinoma, the etiology of the disease and peptide therapeutics for the treatment and prevention of the disease.

Disclosure in the Specification

The specification does not show that any peptides obtained from a protein expressed on human colon carcinoma cells has any of the claimed functional properties, namely, MHC targeting, CTL-induction in order to achieve a therapeutic much less preventative endpoint. The specification does not provide a single working example for any one of the elected peptides much less a protein encoded by human 1-8D interferon inducible gene or a peptide derived therefrom demonstrating that the pharmaceutical composition has one or more of the claimed functional properties in a relevant bioassay or animal model. The specification is not enabling for the peptides being therapeutic or prophylactic because the specification does not show that these molecules could be used for the claimed intended use.

Status of the Prior Art for T-immunogenic, MHC-binding Peptides/ Unpredictability/ Undue Experimentation

In general, the art of synthesizing functional equivalents of naturally occurring proteins is very unpredictable in nature. Although Schirle et al. (J. Immunol. Methods. 2001; 257: 1-16), for example, teaches that several computer algorithms are now available for use in predicting the structures of synthetic peptides that bind MHC molecules, Schirle et al. teaches, "the identified epitopes still have to pass the ultimate

test: they have to prove to be useful in the in vivo situation" (page 11, paragraph bridging columns 1 and 2).

Moreover Anderson et al. (Tissue Antigens. 2000 Jun; 55 (6): 519-531) teaches there is poor correspondence between predicted and experimental binding of peptides to class I MHC molecules; see entire document (e.g., the abstract). Andersen et al. teaches, while knowledge of the peptide binding motifs of individual class I MHC molecules permits the selection of potential peptide antigens, there is no strong correlation between actual and predicted binding when using predictive computer algorithms, and therefore the peptide binding assay remains an important step in the identification of cytotoxic T lymphocyte (CTL) epitopes, which cannot be substituted by predictive algorithms (abstract).

Furthermore, Feltkamp et al. (Mol. Immunol. 1994 Dec; 31 (18): 1391-1401) teaches, while efficient binding of peptide epitopes to MHC class I molecules is required to elicit an immune response against the peptide epitope or the intact antigen, an increased binding affinity does not consistently and reproducibly relate to a peptide epitope's immunogenicity, i.e., its ability to elicit a peptide- and antigen-specific immune response; see entire document (e.g., the abstract). Feltkamp et al. teaches that other factors, in addition to its binding affinity for an MHC molecule, determine whether a peptide epitope, or analogue thereof, will be able to stimulate an effective immune response; see, e.g., the abstract.

With respect to the general state of the art for peptide induction of CTLs, Beier et al. (USPN 2004/0037840; published 2/26/2004; filed 10/26/2001) discloses:

> "It has been clearly demonstrated by several groups that tumour specific cytotoxic T cells (CTL's) are present in many tumours. These CTL's are termed tumour infiltrating lymphocytes (TIL's). However, these cells are somehow rendered non-responsive or anergic by several different possible mechanisms including secretion of immunosuppressive cytokines by the tumour cells, lack of co-stimulatory signals, down regulation of MHC class I molecules etc. There has been many attempts to isolate the tumour specific HLA class I bound peptides recognised by TILs, and in some cases it has also been successful (e.g. peptides from the melanoma associated antigens). Such peptides have been used to induce a tumour specific immune response in the host, but the practical use of tumour specific peptides in vaccines is restricted to a limited segment of the population due to the narrow HLA class I binding specificity of the peptides. Furthermore, it is usually relatively difficult to evoke a CTL response in vivo using synthetic peptides due to the low biological half-life of these substances as well as the difficulties with exogenous priming of MHC class I molecules." [0023-0024]

Applicants have not answered these questions in the specification or advanced our understanding of the status of the art for the inventive peptides with respect to these inherent risks associated with T-cell immunogenic peptides in general.

10. Claims 5, 6 and 59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

See the interpretation of Wands as discussed supra.

Claim 5 is drawn to a peptide derived from a protein encoded by the polynucleotide of residues 31-426 of SEQ ID NO: 58, Claim 6 is drawn to a peptide

derived from a protein encoded by the polynucleotide of SEQ ID NO: 60, and Claim 59 is drawn to an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:61.

The specification discloses the polynucleotides of SEQ ID NOS: 48 and 60 and the polypeptide of SEQ ID NO:61 in two instances at pp. 10 and 18. The specification does not disclose any peptide of from 8 to 10 amino acid residues that could be derived from a protein encoded by the polynucleotides of SEQ ID NO: 48 and 60. Nowhere in the specification do applicants disclose that that any peptide would retain its MHC class I binding ability much less elicit a CTL response. Applicants have not met their burden in showing that any peptides derived from residues 31-426 of SEQ ID NO: 58 and SEQ ID NO: 60 would have any practical use absent a showing that the peptide was inherently operative.

The specification does not disclose any peptides derived from the polypeptide of SEQ ID NO:61. The specification describes the polypeptide of SEQ ID NO: 61 as a sequence polymorphism for the corresponding polypeptide of SEQ ID NO:59. Further, based on the homology between the polypeptides of SEQ ID NO:61 and SEQ ID NO:59, one of skill in the art could not presume that the polypeptides would function similarly under the same circumstances absent evidence to the contrary.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

11. Claims 1, 3, 4, 9 and 12-14 are rejected under 35 U.S.C. 102(e) as being anticipated by Afar et al. (US2005063975, with priority to USPN 6,833,438 and USPN 6,329,503; all of which are cited in the PTO form 892 of 4/12/07).

Claims 1, 3, 4, and 12-14 are drawn to MHC-class I binding, CTL-inducing peptides of from 8 to 10 residues in length and derived from proteins encoded by a polynucleotide expressed in human colon carcinoma cells, where the second residue from the N-terminus and the C-terminal residue are hydrophilic or hydrophobic or neutral, hydrophobic or aliphatic natural amino acids, where the protein is an 1-8D interferon inducbile gene, where the peptide binds to HLA-A2, and where the peptide includes a non-natural modification such as a peptide modification or an N- or C-terminus modification.

Afar discloses MHC-class I binding, CTL-specific, STEAP peptide epitopes obtained from the STEAP protein expressed and encoded by a nucleotide in human colon cancer, where the peptides bind HLA-A2 (Example 9). Afar teaches 8-, 9- and 10 mers containing a leucine at position 2 and a valine or leucine at position 9 (Example 9).

Afar teaches modified peptides conjugated to KHL [0088] and would read on a non-natural modification to the peptide. Further STEAP is an 1-8D interferon inducible gene.

Because the claims are broadly drawn to any peptide derived from any human colon cancer cell, Afar reads on and therefore anticipated the claims.

Conclusion

12. No claims are allowed.

13. A search of commercial nucleotide sequence databases for residues 31-426 of SEQ ID NO: 58 (Claim 4) has identified two references describing a nucleotide with 100% sequence identity (see attached sequence alignments (pp. 1-2)). However, neither reference teaches or suggests that a translated peptide sequence or that the peptide would encode an MHC-Class I binding, CTL-inducing epitope. A search for the polynucleotide of SEQ ID NO: 60 in commercial nucleotide sequence databases did not reveal any nucleotide sequence having 100% identity with the sequence (Claim 6). The closest match at 99.6% is an EST described in WO200259260-A2. A search for the polypeptide of SEQ ID NO:61 in commercial protein sequence databases did not reveal any other proteins having 100% identity. The closest match at 99.1% is a protein described in EMBL/GenBank/DDBJ databases (Q6FH82_HUMAN).

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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